insufficient for the following reasons, each of which will be addressed in turn.

1) In the response of December 10, 2002, Applicants argued that McCarthy et al. does not disclose cleaving at the abasic site to generate an extendible upstream DNA fragment having a 3' hydroxyl terminus. Applicants note that the Examiner's response to this argument is somewhat unclear in the Advisory Action because first the Examiner states that "McCarthy et al. disclose cleaving phosphate linkage at an abasic site in which the 3' hydroxyl terminus is generated." However, instead of citing to a particular portion of McCarthy et al. as is required to support the rejection, the Examiner instead states that it was well known in the art and cites to page 1606, Fig. 1 of Dianov.

These statements by the Examiner in the Advisory Action are unclear and appear contradictory. Firstly, contrary to the assertion of the Examiner, McCarthy et al. do not disclose cleaving phosphate linkage at an abasic site in which the 3' hydroxyl terminus is generated. It appears that the Examiner recognizes this fact despite her comments because she does not cite to McCarthy et al. but instead relies on a citation to Figure 1 at page 1606 of Dianov. However, the novelty of cleaving at an abasic site to generate a 3'OH terminus has never been at issue in the present application.

Cleavage at abasic sites and generation of 3'OH termini was known at the time of the present invention. However, this ability to cleave at abasic sites and generate 3'OH termini is irrelevant to the method used in McCarthy et al. The requirement to cleave of abasic sites to create a 3'OH terminus only becomes relevant in the context of the present invention. Applicants never asserted the invention of cleavage at abasic sites to generate a 3'OH terminus. However, to conclude that this known, but completely irrelevant, process to cleave at abasic sites and generate a 3'OH terminus combines with the other cited references to render the invention obvious requires the improper use of "hindsight reconstruction." "Care must be taken to avoid hindsight reconstruction by using 'the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.'" *Grain Processing Corp. v. American Maize-Prods. Co.*, 840 F.2d 902, 907, 5 USPQ2d 1788, 1792 (Fed. Cir. 1988) (citing *Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1012, 217 USPQ 193, 199 (Fed. Cir. 1983)).

The Examiner further asserts that the claims do not specify which group of the DNA is cleaved; suggesting that the cleavage disclosed in McCarthy et al. would be encompassed by the claims. Applicants respectfully disagree with the Examiner regarding this

point. The claims define what part of the DNA is cleaved in the recitation that the DNA is cleaved "so as to generate and release an extendible upstream DNA fragment having a 3' hydroxyl terminus." This description in the claims dictates where the cleavage occurs. In addition, claim 2 further states that cleavage is on the 5' side of the abasic site.

2) Regarding Chirikjian et al., Applicants argued that the reference discloses the generation of an abasic site at a point of mismatch and that the glycosylase of Chirikjian et al. only recognizes and cleaves mismatches. The Examiner asserts that the claims do not specify whether the abasic site has a mismatch; therefore the glycosylase of Chirikjian et al. would fall within the claims. As discussed previously, the glycosylase of Chirikjian et al. is a mismatch specific glycosylase.

The Examiner suggests that the glycosylase of Chirikjian et al. falls within the scope of the claims because the claims do not specify whether the abasic site has a mismatch. However, this position by the Examiner is scientifically groundless, since there is no such thing as an abasic site having or not having a mismatch, nor is such a thing possible. In addition, the glycosylase of Chirikjian et al. would not be suitable to achieve the present invention.

In Chirikjian et al., the glycosylase is used to excise a mismatched base, thereby resulting in the generation of an abasic site being formed at the site of the excised base. This is what an abasic site is by definition, i.e. a site within a DNA strand where a base is missing on one strand.

With the present invention there is no involvement of mismatches. The glycosylase of the present invention is specific for modified bases and excises them to form abasic sites. There is no relationship in the present invention between the presence of a mismatch and excising a base. The glycosylase of Chirikjian et al. is specific for a mismatch of otherwise normal nucleic acid bases. The present invention, on the other hand, requires the use of a glycosylase that specifically recognizes and cleaves modified bases. Thus, the presence or absence of a mismatch has no bearing on recognition by the glycosylase used in the invention. The specification on page 3 discusses that modified bases are bases that have been made from modified precursor nucleotides. As the Federal Circuit held recently in *All Dental Prodx, LLC v. Advantage Dental Prods., Inc.*, 309 F.3d 774, 64 U.S.P.Q.2d 1945 (Fed. Cir. 2002), the meaning of a claim term may be determined from the specification. It is evident from the specification that "modified" base means for the present invention, bases that have been made from modified precursor nucleotides. As noted, the glycosylase of

Chirikjian et al. does not recognize modified bases, but mismatch bases, which are still normal nucleic acids. As such, the glycosylase used by Chirikjian et al. is completely different from that of the present invention and would not function in the presently claimed method.

As a second point regarding Chirikjian et al., the Examiner notes that the structure of DNA is the same whether the DNA is synthetic or naturally occurring. As such, the synthetic probe of Chirikjian et al. would still be considered a "DNA molecule." However, the Examiner appears to have misunderstood the significance of Applicants' remarks regarding disclosure in Chirikjian et al. The probe in Chirikjian et al. is an exogenously added piece of DNA, regardless of whether it is synthetic or naturally occurring. With the present invention, the extended DNA is an endogenous DNA molecule, i.e. a piece of DNA produced in the reaction of the invention as part of the claimed process. This feature is defined in claim 1 with steps i-iii.

3) The Examiner further asserts that Applicants' arguments regarding Dianov et al. are insufficient because the claims do not specify which side of the DNA is cleaved and how the cleaved product is released. It appears that the Examiner is of the position that

the claims should recite that cleavage is on either the 5' or 3' side of the abasic site as discussed on page 6 of the December 10, 2002 response. However, regardless of which side of DNA is cleaved and how the cleaved product is released, the same resulting product of a 3'OH group on the upstream fragment is achieved. This feature is illustrated in Figure 1, wherein "A" is the end product regardless of whether the intermediate is "B" or "C."

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact MaryAnne Armstrong, PhD (Reg. No. 40,069) at the telephone number of the listed below.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a two (2) month extension of time for filing a reply in connection with the present application, and the required fee is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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